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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/589,589 | Applicant(s) HIGH ET AL. | |
|---|---|---|---|
| | Examiner Brian Whiteman | Art Unit 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 12-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 June 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### Final Rejection

Claims 1-10, 12 and new claims 13-29 are pending examination.

Amendment to claims 1-6, 9; the addition of claims 13-29, and applicants' traversal is acknowledged and considered.

### *Drawings*

**NOTE**: In the next response, please submit a response to the PTO 498 because a PTO 498 was filed with the non-final rejection dated 11/8/01 and the applicants did not submit proposed corrections or corrected drawings with paper no. 13. If the reply to the Final Rejection does not have a response to the PTO 498, the response will be considered non-responsive. See 37 CFR 1.85(a).

The non-elected species in claims 4 and 9 are re-joined with the elected species because the prior art does not teach nor suggest a method of preventing the formation of inhibitory antibodies to a protein. However, the non-elected species in new claims 16 and 21 are considered to be still drawn to non-elected species because the rejection for a method of reducing the formation of inhibitory antibodies to a protein comprising using Factor IX and cyclophosphamide remain. See the rejections below.

This application contains claim 11 drawn to an invention non-elected claim with traverse in Paper No. 11. A complete reply to the final rejection must include cancellation of non-elected claim or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13, 15, 24, 26, and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A method of preventing the formation of inhibitory antibodies to a Factor IX protein delivered to a mammal by way of gene therapy, wherein the method comprises:

a) administering cyclophosphamide (Cyp) multiple times to a mammal undergoing gene therapy; wherein one administration of Cyp is administered at around the time the gene therapy is administered;

b) the gene therapy is delivery of Factor IX using an adeno-associated virus vector; and

c) the gene encoding the delivered Factor IX protein is from the same species as the mammal.

2) A method of preventing the formation of inhibitory antibodies to a Factor IX protein delivered to a mammal by way of gene therapy, wherein the method comprises:

a) administering anti-CD40 ligand multiple times to a mammal undergoing gene therapy; wherein one administration of anti-CD40 ligand is administered at around the time the gene therapy is administered;

b) the gene therapy is delivery of Factor IX using an adeno-associated virus vector; and

c) the gene encoding the delivered Factor IX protein is from the same species as the mammal.

3) A method of reducing the formation of an inhibitory antibody to Factor IX protein delivered to a mammal by way of gene therapy, wherein the method comprises

a) administering to the mammal an immunosuppressive agent in conjunction with the gene therapy, wherein the gene therapy comprises delivery of a nucleic acid encoding Factor IX to the mammal, which when expressed in the mammal, an increase in the level of Factor IX in the mammal is observed; and does not reasonably provide enablement for the rest of the disclosure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The field of the invention lies in preventing the formation of antibodies in a mammal undergoing gene therapy, wherein said method comprises administering to said mammal an immunosuppressive agent in conjunction with said gene therapy. Specifically, the claimed invention encompasses preventing inhibitory antibodies in mammal undergoing gene therapy for factor IX, said method comprising administering to said mammal cyclophosphamide in conjunction with said gene therapy.

The state of the art for gene therapy as exemplified by Rubanyi (Molecular Aspect of Medicine, Vol. 22, 2001, pages 113-142) teaches that:

> The most promising areas for gene therapy today are hemophilias and cardiovascular diseases. This is based on the relative ease of access of blood vessels for gene therapy, and also because existing gene delivery technologies may be sufficient to achieve effective therapeutic benefits for some of these indication (transient expression in some but not all affected cells is required to achieve a therapeutic effect at a relatively low does of vector) (abstract). For

> other diseases (including cancer) further development in gene delivery vectors and gene expression systems will be required. It is important to note, that there will not be a universal vector and each clinical indication may require a specific set of technical hurdles to overcome. These will include modification of viral vectors, engineering of non-viral vectors by mimicking the beneficial properties of viruses, cell-based gene delivery technologies, and development of innovative gene expression regulation systems (abstract).

Furthermore, Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,
2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;
3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and
4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (Anderson, *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that

factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

In further support of Rubanyi about the predictability for treating hemophilia in a mammal is exemplified by High et al (Applicants' IDS, US Patent No. 6,093,392), High teaches that one viral vector, adenovirus, has been used to effect expression of high levels of canine factor IX in immunodeficient/immunocompetent mice when the virus is administered in conjunction with immunosuppressive agent (column 1, lines 36-40). High uses a recombinant AAV vector comprising of factor IX (F.IX) to treat hemophilia in a mammal. Also, retroviral vectors have also been used experimentally a model for treatment for hemophilia B. However, levels of expression FIX from these vectors are reported to be too low to be of therapeutic value (column 1, lines 59-63). Plasmid DNA which has been injected into mouse muscle has been shown to direct expression of erythopoietin (Epo), but this method of gene therapy is not efficient for the expression of a gene product such as F.IX which is needed at relatively high levels in the circulation (compared with Epo) to achieve a therapeutic effect (column 1, lines 64-column 2 line 4).

The specification teaches a method for inhibiting the formation of inhibitory antibodies in a murine knockout model of hemophilia B undergoing gene therapy treatment, said method comprising administering to said mouse a recombinant AAV vector comprising murine factor IX (mFIX) in conjunction with anti-CD40L,

cyclosporin A, or cyclophosphamide (pages 13-16). The results display that mice injected with AAV mFIX make antibodies, which are inhibitory to the transgene product (page 15). Also, the results show that transgene expression may be increased with using an immunosuppressive agent in conjunction with delivering AAV comprising mFIX to the mice (pages 14-16). The state of the art for using immunosuppressive agents to prevent neutralizing antibodies against a transgene product as exemplified by Potter et al., Ann NY Acad Sci, Vol. 875, pages 159-174, 1999, Potter teaches that:

> The response of a recipient to various immunosuppressive agents can be classified into three categories. The first category, shown by treatment with CTLA4-Ig or interleukin-12, was similar to the untreated controls, no suppression of anti-hGH antibodies and no significant improvement in delivery of hGH. The second category of response observed in four treatment protocols (cyclophosphamide, FK506, anti-gp-39, and interferon-γ), was suppression of antibodies but no improvement in sustaining delivery of transgene product. It is clear that while these treatments are more effective in antibody suppression than CTLA4-Ig and IL-12, they were unable to exert sufficient suppression of the humoral response to permit a sustained level of circulating recombinant hGH produced by the encapsulated cells. The last category of response was seen in the group of mice receiving anti-CD4; strong antibody suppression and the most sustained hormone delivery. See pages 171-172.

In addition, the specification provides working examples encompassing a method where mice administered FK506 in combination with murine Factor IX delivered via gene therapy exhibited shorter aPTT times than mice not treated which were not treated with FK506 (page 15, Figure 5). However, the specification does not display any antibody titer for the mice administered FK506. In addition, at the time the invention was made, the art of record and the as-filed specification were absent for

how correlating shorter aPTT times is considered an acceptable model for preventing antibodies to a protein delivered to a mammal by way of gene therapy, it would take one skilled in the art an undue amount of experimentation to reasonably correlate shorter aPTT to any method of preventing the formation of inhibitory antibodies in a mammal undergoing gene therapy in conjunction with any other immunosuppressive agent. Furthermore, Herzog (Molecular Therapy, Vol. 4, pp. 192-200, 2001) states that:

> The risk of inhibitor formation in gene therapy may also be influenced by the particular type and design of vector, the route of administration, the underlying F9 mutation and genetically determined characteristics of the patient's immune system. Studies that help define the risk and identify factors that may reduce or eliminate it can be designed using relevant animal models and vectors expressing species-specific transgenes (pages 193 and 198).
> Transient immunosuppression around the time of vector administration was sufficient to prevent an immune response that could block long-term expression (page 196).
> These responses are likely different from those more typically observed in the context of other vectors such as adenovirus (which is dominated by a Th1-driven response that is clearly distinct from antibody formation in the context of protein therapy. While, immunoglobulin subclass analysis supports the interpretation of an analogy between mouse and canine studies, further analysis of T lymphocyte responses will be required to draw a firm conclusion (page 198).

Thus, Herzog further emphasizes the unpredictability taught by Potter for making and using the full breadth of the claimed invention. The as-filed specification does not provide sufficient guidance because of the unpredictability taught by Potter for what immunosuppressive agent in conjunction with gene therapy will prevent antibodies to a protein for one skilled in the art to observe an improve expression of the protein and by Herzog, who states that, "the complexity of the immune response to a secreted transgene product influences the design of studies to address these issues for a given

combination of a specific vector and route of administration (page 198)." Also, one skilled in the art could not reasonably extrapolate the working examples in the specification in view of the art of record to preventing the formation of inhibitory antibodies in any mammal undergoing gene therapy using any immunosuppressive agent other than Cyp and anti-CD40L without an undue amount of experimentation. Therefore, the claimed invention is not enabled for a method of preventing the formation of inhibitory antibodies in a mammal undergoing gene therapy in conjunction with gene therapy other than 1 and 2 listed above.

Furthermore, in view of the In re Wands Factors, claim 3 and new claim 15 are not enabled by the specification, which provides sufficient guidance for one skilled in the art to make and use a method of inhibiting or preventing antibodies in a mammal undergoing gene therapy, wherein the method comprises administering to said mammal an immunosuppressive agent in conjunction with said gene therapy and the transgene is from the same species of said mammal. The specification displays an increase in Factor IX in mouse undergoing gene therapy in conjunction with an immunosuppressive agent (cyclophosphamide). Since the specification does not define the breadth of the term "beneficial effect", one skilled in the art of gene therapy would interpret that the breadth of the term "beneficial effect" to encompasses complete correction of a genetic defect. However, in view of the breadth of the claims, the specification does not provide sufficient guidance for one skilled in the art to make and use the method described above for producing a beneficial effect (e.g. complete correction) in a mammal undergoing Factor IX gene

therapy since High teaches that F.IX is needed at relatively high levels in the circulation to achieve a therapeutic effect (IDS, column 1). Thus, the as-filed specification fails to provide sufficient guidance for one skilled in the art to reasonably extrapolate from using increasing the level of factor IX in a mouse using a mouse Factor IX transgene, in conjunction with an immunosuppressive agent to producing a beneficial effect (complete correction of the disorder) in any mammal in view of the doubts expressed above by Anderson, Rubanyi, and Verma, and the lack of guidance provided by the specification at the time the application was filed.

Thus, in view of the In Re Wands Factors, listed above, the quantity of experimentation required due to the lack of direction provided by the as-filed specification for using gene therapy to produce a beneficial effect in a mammal, the working examples encompass increasing the level of Factor IX in a knock-out mouse model of factor IX in conjunction with cyclophosphamide; the state of the gene therapy was considered predictable when trying to increasing the level of a transgene in a mammal with a genetic disorder (e.g. hemophilia B) that does not require precise gene expression, the relative skill of those in the art, and the breadth of the claims; the as-filed specification fails to provide sufficient guidance for how to produce a beneficial effect (e.g. complete correction) in any mammal.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable 1-3 listed above. Given that gene therapy wherein any carrier is employed to correct a disease (beneficial effect) or a medical condition in any mammal was unpredictable at the time

the application was filed, and given the lack of sufficient guidance as to which immunosuppressive agent can prevent the formation of antibodies to a protein delivered by way of gene therapy using any gene delivery vector cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicants' disclosure and the unpredictability of gene therapy.

Applicants assert that the specification enables the claim, as originally filed and as presently amended for the following reasons: the claims are directed to preventing or reducing the formation of antibodies to a protein delivered to a mammal by way of gene therapy so applicants need not address any grounds of rejection relating to the alleged difficulties associated with gene therapy; if an immunosuppressive agent does not prevent or reduce formation of an antibody in a particular context than the immunosuppressive agent is not encompassed within the claim; Accordingly, that some immunosuppressive agents may not reduce or prevent formation of antibodies as discussed by Potter et al. is irrelevant to enablement of Applicants' claims since such agents would not be included in the claims, The specification exemplifies three different immunosuppressive agents that are able to prevent or reduce formation of inhibitory antibodies against a protein delivered by way of gene therapy (pages 13-15); Exhibit A demonstrates that the working example can be extrapolated to other mammals because Herzog et al. display that the same protocol used in the specification was used in dogs. Pages 6-10.

Applicants' traversal is acknowledged and is found partially persuasive for 1-3 listed above. However, the traversal is not found persuasive for the rest of the claimed embodiment for the following reasons: The specification provides working examples encompassing a method of preventing and/or reducing inhibitory antibodies to a Factor IX protein in a murine model of

Factor IX undergoing Factor IX gene therapy using different protocols comprising of multiple administrations of either cyclophosphamide (Cyp) or anti-CD40L (pages 13 and 14). The traversal also points out that when using either agent, Factor IX antibodies in the mice were either significantly reduced or were undetectable (page 14). The traversal further states that, "mice administered FK506 in combination with murine Factor IX delivered via gene therapy exhibited shorter aPTT times than mice not treated which were not treated with FK506 (page 15, Figure 5). However, the specification and/or the applicants' traversal do not display any antibody titer for the mice administered FK506. In addition, at the time the invention was made, the art of record and the as-filed specification were absent for how correlating shorter aPTT times is considered an acceptable model for preventing antibodies to a protein delivered to a mammal by way of gene therapy, it would take one skilled in the art an undue amount of experimentation to reasonably correlate shorter aPTT to a method of preventing inhibitory antibodies to Factor IX.

Furthermore, with respect to Exhibit A (Herzog et al.), Herzog displays partial correction of coagulation parameters in a canine model of Hemophilia B using Cyp at different times in conjunction with one administration of AAV.FIX. Herzog uses a different time point to administer the Cyp than the time points used in the method displayed in the specification (instead of 0, 2 weeks, 4 weeks, and 6 weeks for Cyp, Herzog administered Cyp at day 0, and bi-weekly up to 6 weeks). Herzog states that:

> The risk of inhibitor formation in gene therapy may also be influenced by the particular type and design of vector, the route of administration, the underlying F9 mutation and genetically determined characteristics of the patient's immune system. Studies that help define the risk and identify factors that may reduce or eliminate it can be designed using relevant animal models and vectors expressing species-specific transgenes (pages 193 and 198).

> Transient immunosuppression around the time of vector administration was sufficient to prevent an immune response that could block long-term expression (page 196). These responses are likely different from those more typically observed in the context of other vectors such as adenovirus (which is dominated by a Th1-driven response that is clearly distinct from antibody formation in the context of protein therapy. While, immunoglobulin subclass analysis supports the interpretation of an analogy between mouse and canine studies, further analysis of T lymphocyte responses will be required to draw a firm conclusion (page 198).

Thus, Herzog displays that Cyp in conjunction with Factor IX gene therapy can prevent inhibitory antibodies to a Factor IX protein delivered to a mammal. However, Herzog further emphasizes the unpredictability taught by Potter for making and using the full breadth of the claimed invention. The traversal and the as-filed specification do not provide sufficient guidance and/or factual evidence for how to overcome the unpredictability stated by Herzog and Potter (For Potter, see 112 enablement rejection above). Herzog states that, "the complexity of the immune response to a secreted transgene product influences the design of studies to address these issues for a given combination of a specific vector and route of administration (page 198)." In addition, the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [footnote omitted].

On this record, it is apparent that the specification and the applicants' traversal (See page 8 of traversal, which states, "if an immunosuppressive agent does not prevent or reduce the formation of antibodies in a particular context than the immunosuppressive agent is

not encompassed within the claims") provide no more than a plan or invitation in view of the art of record exemplifying the unpredictability of using any immunosuppressive agent in conjunction gene therapy for preventing inhibitory antibodies, for those skilled in the art to experiment with immunosuppressive agents so as to provide preventing inhibitory antibodies against a protein expressed by a way of gene therapy as intended by the as-filed specification at the time the invention was made.

See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification; the specification does not provide reasonable detail for what protocols are required for different immunosuppressive agent in conjunction with gene therapy other than cyclophosphamide or anti-CD40 ligand for preventing the formation of inhibitory antibodies to a protein, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the scope listed above to the full breadth of claimed invention. Therefore, the as-filed specification is only enabled for 1-3.

In addition, the Exhibit A, which is a post-filing article (2001, two years after the provisional was filed, 6/8/99) displaying partial correction of Factor IX using the method in the claimed invention in canine hemophilia B caused by a null mutation was not known at the time the invention was made.

Furthermore, applicants assert that the rejection for claim 3 and new claim 15 (because claim 15 parallels claim 3) under 112 enablement should be withdrawn because complete correction of a genetic defect is not required in order to enable the claim; amendment to claim 3 to recite the protein delivered is Factor IX, which produces a beneficial effect; Exhibit A and the specification demonstrate that Factor IX levels sufficient to produce a beneficial effect can be attained in a mammal. See pages 9 and 10.

Applicants' traversal is acknowledged and is not found persuasive for the following reason: the breadth of the term "beneficial effect" is not defined by the specification or by the art of record. Therefore, in view of the definition of the term "beneficial", the term encompasses complete correction. The specification displays that level of Factor IX was increased in mouse using the claimed method and does not provide sufficient guidance in view of the art of record for how an increase level reasonably extrapolates to a beneficial effect other than increasing the level of Factor IX. Therefore, at the time the invention was made, the claimed invention was only enabled for using the method of the claimed invention for increasing the level of Factor IX in a mammal undergoing Factor IX gene therapy.

Applicants request that the rejections under 112 second be withdrawn because of the amendment to claims 4 and 6.

Applicants' traversal is acknowledged and is found persuasive. However, in view of the amended claims, a new rejection under 112 second follows:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 13 recite the limitation "said gene". There is insufficient antecedent basis for this limitation in the claim.

***Claim Rejections - 35 USC § 102***

Applicants request that the rejection for claims 1-10 and 12 under 102(b) and (e) be withdrawn because the claimed invention is directed to a method of preventing or inhibiting the formation of antibodies to a protein delivered to a mammal by way of gene therapy and the rejections describe suppression of an immune response against adenovirus gene delivery vehicle. Thus, the rejections fail to disclose each element of the claimed invention as required under 102. See pages 10-12.

Applicants' traversal is acknowledged and is found persuasive because of the amendment to claims to encompass gene being the same species as the said mammal.

Therefore, the rejections under 102 are withdrawn.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13-23, 25, 27, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over High et al. (Applicants IDS, US Patent No. 6,093,392) in further view of Smith et al. (Gene Therapy, vol. 3, 1996, pages 496-502). High claims a method of treating hemophilia in a mammal comprising: a) providing a recombinant AAV comprising a nucleic acid encoding Factor IX; and administering an amount of said AAV to a mammal wherein said factor IX is expressed at levels having a therapeutic effect on said mammal (column 29, claim 1. In addition, High teaches that adenoviral vectors are well known in gene therapy and have been used to effect expression of high levels of canine factor IX in immunodeficient/immunocompetent mice when the virus is administered in conjunction with immunosuppressive agent (column 1, lines 36-40).

High further teaches administering AAV.FIX to a dog that has a point mutation in the catalytic domain of Factor IX, appears to render the protein unstable, suffer from severe hemophilia B (column 18, lines 25-65 and column 19, lines 35-60). However, High does not specifically teach a method of reducing formation of antibodies to a protein delivered by way of gene therapy, wherein the method comprises administering to the mammal an immunosuppressive agent in conjunction with the gene therapy, wherein a gene encoding the delivered protein is from the same species as the mammal.

However, at the time the invention was made, Smith teaches that multiple intravenous administration of adenovirus vectors resulting transgene expression can be accomplished in immune competent animals treated with a short course of immunosuppression at the time of vector delivery (pg. 499, 1st paragraph under discussion). More specifically, Smith demonstrates that the humoral immune response to a systemically administered adenovirus vector is dose dependent and can be modulated by a brief treatment with the immunosuppressive agent cyclophosphamide (Cyp) at the time of the initial treatment. This strategy permits effective multiple repeat doses of a vector encoding a therapeutic gene such as Factor IX (pg. 496).

It would have been obvious for a person of ordinary skill in the art to use an immunosuppressive agent (e.g. Cyp) to reduce the inhibitory antibodies to a Factor IX protein or vector delivered to a mammal by way of gene therapy. One of ordinary skill in the art would have been motivated to employ Cyp in the method because the administration of Cyp would reduce the mammal's immune response to both the vector and the protein, which would result in an increase expression of the protein. Furthermore, this demonstrates that employing the immunosuppressive agent, cyclophosphamide, in conjunction with a method of gene therapy for

treating hemophilia to increase the efficiency of gene transfer and the expression of the nucleic acid encoding the protein Factor IX in a mammal was obvious by High in view of Smith. Absence evidence to the contrary, High in view Smith use the same method and materials as contemplated by the as-filed specification and the method would have resulted in intrinsically inhibiting the formation of inhibitory antibodies specifically binding with the transgene being expressed in said mammal.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicants' traversal is acknowledged and is not found persuasive for the following reasons: Applicants have not provided sufficient guidance or factual evidence that High in view Smith did not use the same materials as contemplated by the as-filed specification and that the method comprising the same materials would not have resulted in intrinsically inhibiting the formation of inhibitory antibodies specifically binding with the protein being expressed in said mammal.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0198.

Brian Whiteman
Patent Examiner, Group 1635

6/3/02

DAVE T. NGUYEN
PRIMARY EXAMINER